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Formation of Glycogen after taking Different Varieties of Sugar.

AN ABSTRACT.

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FORMATION OF GLYCOGEN

AFTER TAKING DIFFERENT VARIETIES OF SUGAR.

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By GRAHAM LUSK, Ph. D.,
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There are two theories regarding the formation of the curious substance called glycogen, which is found deposited in various organs of the body, and especially in the liver cells.

According to one theory, known as the "anhydride theory," dextrose and those sugars which are changed into dextrose in the intestinal canal are transformed into the anhydride of dextrose or glycogen by the activity of the liver cells. This theory arose because large quantities of glyco-

* Ueber die Glycogenbildung nach Aufnahme verschiedener Zuckerarten. Nach den Versuchen der Herrn Dr. Jac. G. Otto aus Christiania Dr. A. C. Abbott aus Baltimore, Dr. Graham Lusk aus New York, und Dr. Fritz Voit aus München. Zusammengestellt von Carl Voit. (Aus dem physiologischem Institut zu München.) *Zeitschrift für Biologie*, vol. xxviii, p. 245, 1892.

Also, *Ueber die Glycogenbildung bei Aufnahme verschiedener Zuckerarten.* Von Graham Lusk. Dissertatio inauguralis. München, 1892.

gen were always found in the liver after feeding dextrose, lævulose, and cane sugar.

The second theory maintains that the glycogen is derived from the continually decomposing albumin. So long as no sugars reach the blood from the intestinal canal, this glycogen is swept away by the blood current as soon as formed and contributes to fulfill the conditions for combustion in the cells. When, however, sugars are introduced into the blood, they burn in preference to the less easily decomposable glycogen, and hence the glycogen accumulates in the organization. The more easily combustible sugars protect or "economize" the less combustible glycogen. This, then, is the "economy theory."

Wollfberg especially showed the economy theory to be true in certain cases. Experimenting upon hens, he found, on feeding to them a constant amount of carbohydrates with varying amounts of albumin, that the glycogen stored in the liver increased with the amount of albumin given. The principal proof apparently emanated from Luschinger and others, who showed that chemically the glycogen was always the anhydride of dextrose. Maydl asks how a ketone (lævulose) can go over into an aldehyde (dextrose).

At one time there was general acceptance of the "economy theory." Sugar burned most easily, glycogen next, and fat with the greatest difficulty; hence sugar economized the glycogen formed from the decomposition of albumin, while glycogen burned in advance of the fat. Therefore we see why ingestion of the less combustible fat does not affect the amount of glycogen stored.

In the students' exercises held by Professor Voit, it has been customary to feed rabbits, which had been starved several days, with a large quantity of sugar (sixty grammes of cane sugar in solution), and, after eight hours, to kill the rabbits and demonstrate the glycogen in the liver. The

amounts found varied from four to nine grammes, and ran as high as twelve per cent. of the fresh, or forty per cent. of the dry, substance of the liver.

The possibility of producing so large a quantity of glycogen in so short a time brought up the question whether this large amount could have been produced from the decomposition of albumin during the same eight hours. Erwin Voit fed a goose for five days on rice, and the amount of glycogen found in the liver at the end of the experiment proved to be three times greater than what could possibly have been derived from the albuminoid decomposition of the whole five days. Some of the ingested carbohydrates must have been changed directly into glycogen. Here we have a proof of the anhydride theory, but by no means a refutation of the economy theory. Indeed, Külz has indisputably shown that glycogen could be produced from albumin. We see, therefore, that the ingested carbohydrates first "economize" the glycogen produced from albumin, and afterward, when present in large quantities, are themselves directly changed into glycogen by a process of dehydration. The truth of both theories, then, seems to be established.

These facts cause us to consider (1) what kinds of sugar are directly convertible into glycogen, (2) what kinds merely "economize" the albuminoid glycogen, and (3) why it is that one and the same glycogen is always produced, even after the ingestion of the most varied kinds of sugar. Professor Voit therefore instituted feeding-experiments with dextrose, cane sugar, maltose, lævulose, milk sugar, and galactose. The animals fed were rabbits and fowls. They were starved from four to six days, when the amount of glycogen in the organization seldom exceeds unweighable traces. Then, eight hours after ingestion of the sugar solution, the animal was killed and the liver treated for analysis.

Experiments made by various authors show that in a starving rabbit the amount of glycogen possibly obtainable from eight hours' decomposition of albumin can not exceed 0·66 to 1·52 gramme; in the case of fowls, 0·19 to 2·29 grammes. Amounts of glycogen, therefore, which do not overstep these limits can be attributed to the albumin and not to an ingested material.

The following table shows the amounts of glycogen we found after ingestion of the various sugars named:

Kind of Sugar.	Weight of glycogen in liver.		Per cent. of glycogen in liver.	
50 grammes dextrose, fowl (Otto)	5·37	7·3	15·3	16
80 " " rabbit (Otto)	9·27		16·8	
60 " cane sugar, fowl (Otto)	4·94	5·5	13·3	10
55 " " rabbit (Otto)	4·35		7·4	
60 " " " (Otto)	8·50		12·0	
30 " " " (Lusk)	4·06		6·5	
54·8 " lævulose, fowl (Otto)	3·99	4·6	10·5	10
54·8 " " rabbit (Otto)	5·27		9·1	
60 " maltose, fowl (Otto)	4·07	4·1	10·4	9
60 " " rabbit (Otto)	4·13		8·1	
55 " galactose, fowl (Otto)	0·67	0·8	1·3	1
68·2 " " rabbit (Otto)	0·87		1·5	
32 " milk sugar, fowl (Otto)	0·12	0·8	0·2	1
48 " " rabbit (Otto)	0·87		1·7	
32 " " " (Otto)	0·14		0·4	
.. " " " (Otto)	....		0·9	
50 " " " (Abbott)	....		0·7	
50 " " " (Abbott)	....		1·2	
50 " " " (Abbott)	....		1.5	
50 " " " (Lusk)	2·18		3.6	

A review of the above table demonstrates indisputably that large doses of galactose and milk sugar bear an entirely different relation to the formation of glycogen to that exhibited by dextrose, cane sugar, lævulose, and maltose. The latter four produce glycogen in large amounts, whereas the amount produced after feeding with milk sugar and galac-

tose is so small as to be derivable from the decomposition of albumin. Not only our investigations, but likewise those of Külz, confirm these same relations.

How, then, are we to explain the large quantity of glycogen found after feeding dextrose, cane sugar, lævulose, and maltose? Perhaps the last-named three are transformed into dextrose in the intestinal canal. It has long been known that large quantities of sugar ingested produce an excretion of sugar in the urine, and from the variety of sugar excreted we may form some idea of what has gone on in the body. We therefore turn to the consideration of the behavior of the different sugars in the intestinal tract and their emission in the urine.

Cane sugar certainly is transformed, in part, into dextrose. Professor Voit has for thirty years shown in his lectures that a 0·3-per-cent. hydrochloric-acid solution at the body temperature quickly changes cane sugar into a mixture of lævulose and dextrose—*i. e.*, invert sugar. Certain ferments have the same action. The writer once gave a rabbit sixty grammes of cane sugar and killed the animal six hours afterward. He found twenty times more invert sugar than cane sugar present in the intestines. Hence we may conclude that a considerable amount is absorbed as dextrose. Because much cane sugar is found in the urine, it by no means proves that all the ingested cane sugar is absorbed as such; it could easily be that cane sugar is less readily burned, or, one may reason, that perhaps it may not be converted into glycogen, and in this way be removed from the circulation. It is probable that the greater part of the cane sugar is absorbed as invert sugar, from which the glycogen is manufactured.

Lævulose remains unchanged in the intestines, is absorbed as such, and in extreme cases is emitted in the urine (Otto, Fritz Voit). The lævulose given was nearly pure, and destructible by boiling with ten-per-cent. hydrochloric acid. In the intestinal contents, and in the urine of the animals experi-

mented upon, the sugar found was equally so destructible Dextrose would not have been destroyed.

Maltose is, with dextrine, a product of the action of dilute acids on starch paste, which action, if prolonged, yields dextrose. Certain ferments have the power of changing starch into maltose and dextrine, and then finally into dextrose. The pancreatic and intestinal juices possess this power to a high degree. Maltose, therefore, is transformed into dextrose in the intestinal canal.

Galactose is probably absorbed unchanged.

Milk sugar, like galactose, produces no large amount of glycogen, and hence it was inferable that it did not break up into a mixture of dextrose and galactose (into which constituents it can be converted by treatment with acids). If the decomposition did take place in the intestines, then the dextrose formed must ferment with yeast, and our investigations are based upon this fact. Dr. Abbott made the preliminary experiments, and, with great diligence and patient labor, devoted himself to the solution of the problem. In his experiments he used the ordinary commercial yeast, and noticed that the solutions obtained from the intestines treated with this yeast rapidly decreased in their percentage of sugar, and after a few days the whole of the sugar had disappeared. The results were at first apparently inexplicable, but the cause was the presence of foreign bacteria (probably lactic fermentation). Some months after the unavoidable departure of Dr. Abbott from Munich the writer took up the subject, using a culture of pure yeast (*Saccharomyces apiculatus*). The result of the investigations was to establish the fact that milk sugar undergoes no change in the intestines, and is emitted unchanged in the urine.

It is evident that cane sugar and maltose form dextrose in the intestinal canal; that lævulose, milk sugar, and probably also galactose, do not form dextrose, but are absorbed unchanged. But ingestion of lævulose produces a large store of glycogen in the body. Hence, not only dex-

trose is converted into glycogen, but lævulose must also undergo the same change.

Now, if cane sugar and maltose form glycogen only in virtue of the fact that the intestines change them into dextrose, by excluding the factor of the intestinal tract they should not produce glycogen. The factor of the intestinal tract could be obviated by subcutaneous injection, in which way we were able to bring considerable amounts of sugar into the circulation. Then, again, lævulose, milk sugar, and galactose, when introduced by subcutaneous injection directly into the tissues of the body, should form glycogen only in the event that the liver itself has the power to turn them into dextrose.

These experiments consisted in the subcutaneous injection of the different sugars, and were performed by the writer upon starving rabbits. Fifty grammes of the sugar was dissolved in water to form 150 c. c. solution, and 10 to 15 c. c. were injected at intervals of about an hour for ten hours. The animal was afterward left quietly for five hours, and then killed. The average of glycogen obtained is given below; in each case two or more experiments were made:

	Grammes of glycogen in liver.	Per cent. of glycogen in liver.
50 grammes dextrose............	3·5	5·0
55 " cane sugar..........	0·4	0·7
50 " lævulose............	5·5	5·9
50 " milk sugar..........	0·3	0·8

This table, showing results after the subcutaneous injection of the various sugars, exhibits very striking differences. It is evident that dextrose produces much glycogen, and cane sugar little. Hence the large amount of glycogen found after cane sugar has been taken into the in-

testines is in virtue of its change there into invert sugar—*i. e.*, a mixture of dextrose and lævulose. Maltose probably acts like cane sugar. Milk sugar shows little increase in the glycogen stored, and therefore can not be converted into dextrose. On the contrary, large quantities of glycogen, even as high as 9·1 per cent., were found after subcutaneous injection of lævulose. There can be but one conclusion, therefore, and that is that the liver cells have the property of transforming lævulose either into dextrose, or directly into the anhydride of dextrose, glycogen. Emil Fischer showed a few years ago that dextrose could be made from lævulose in the laboratory. This is now seen to have its counterpart in the animal kingdom. Entirely analogous to this is the preparation of milk sugar from dextrose in the glands of the breast.

It is remarkable that only the two fermentable sugars, dextrose and lævulose, are convertible into glycogen. The liver cells manufacture glycogen from these two sugars only.

In plants there are similar transformations. Arthur Mayer, working in Göttingen, has shown that leaves make starch of dextrose, of lævulose, and galactose. Also vegetable starch is made from mannite, dulcite, and maltose.

The importance of glycogen for the animal organization is that of a transitory, reserve material.

There is usually taken, at an ordinary meal, an excess of albumin, fat, and carbohydrates, over and above the immediate needs of the body. This excess must not remain in the blood, as there it would disturb the processes in the cells, or it would be excreted in the urine. The cells are not able to decompose this excess in a short time, and even if this were possible, more energy would thus be liberated than necessary for the needs of the body in the time given.

To obviate these disturbances, the excess is deposited in a less combustible form and in a less readily accessible place. The soluble circulating albumin of the blood is, to some extent, deposited as systemic albumin in the substance of the body; the fat is deposited in the fatty tissue, and the sugar is deposited in various organs of the body, especially in the liver cells, as the less diffusible, less decomposable glycogen.

We know that the facts go to prove that albumin is broken up in the body into a nitrogenous portion and a non-nitrogenous portion. The investigations of Feder show that in a dog the greater part of the nitrogenous portion of the albumin consumed is already excreted in the first fourteen hours, while the non-nitrogenous portion requires twenty-four hours for its combustion. This first decomposition of albumin into a nitrogenous and a non-nitrogenous portion is not accompanied by the liberation of much energy, as, in the few hours of this decomposition, more energy would be set free than needed. The principal source of energy comes, therefore, from the non-nitrogenous portion, just as it is also found in the non-nitrogenous sugar and fat. The temporary excess of the non-nitrogenous portion of the albumin, as well as the excess of food sugar and fat, are deposited in the body as fat and glycogen, and then, in the course of twenty-four hours, gradually re-enter the blood current and are burned in the cells. In this way the glycogen produced is always swept away again in amounts dependent upon the needs of the cells.

The first demonstration of glycogen by Claude Bernard was little more than play with an interesting toy. Experiments since have shown that the transformation of the easily combustible sugars into the less combustible glycogen is at once one of the most wonderful and one of the most important arrangements in the animal organization.

In closing this article, and in furnishing the American profession with the principal results of these latest views and investigations of Professor Voit, the writer takes the opportunity to express his deep gratitude to his great teacher, and his high personal admiration for him developed during long contact in the laboratory.